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Homeostatic and Circadian Abnormalities in Sleep and Arousal in Gulf War Syndrome

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14. ABSTRACT
The purpose of this study is to assess sleep and wake parameters in veterans of the first Gulf War who have fatigue and other symptoms compared with veterans who do not have fatigue utilizing novel assessment techniques including temperature and high density EEG. This research study is in the data collection phase. The most significant finding in this study during the research period is that temperature curves, which are well-tied with sleep/wake and feelings of fatigue/alertness are showing different projections in veterans endorsing fatigue than those who do not. Additionally, we continue to find that the time course of slow wave activity (SWA) may be different in subjects endorsing fatigue compared to those who do not. Slow wave sleep is often thought to play a role in the recovery and restorative aspects of sleep.

15. SUBJECT TERMS
Dense array EEG, temperature, melatonin, vigilance

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Introduction

This research project assesses sleep and wake parameters in veterans of the first Gulf War who have fatigue and other symptoms compared to veterans who do not have fatigue. It utilizes novel assessment of brain waves with high density EEG, which allows for high spatial and temporal resolution to provide a window into how sleep is regulated at the global and local level. This will allow us to determine how specific sleep pattern activity is altered in veterans with fatigue. Beyond the typical overnight polysomnography, this assessment includes objective wave analysis of slow wave characteristics, origin and propagation. Circadian rhythm is also assessed, including temperature and salivary melatonin measures, as well as salivary cortisol levels. Vigilance at various points is tested with a psychomotor vigilance test, and there is an optional genetic testing part of the study to assess many polymorphisms that have been associated with other fatiguing conditions and symptoms.

Body

In the Statement of Work, we anticipated being in the recruitment and running subjects in the protocol phase, which is where we are currently. We have successfully completed 14 subjects in our study at this point. We are continuing to recruit subjects.

Data collected includes core, peripheral and distal body temperature, two nights of dense array EEG, multiple symptom scales involving fatigue, pain, and other symptoms, cortisol samples to be able to note diurnal changes, as well as morning cortisol rise from natural wake. We also have collected melatonin samples in a low light environment to be able to assess dim light melatonin onset. Psychomotor vigilance task (PVT) data has been collected at various points in the day in concert with subjective fatigue and sleepiness data.

All comments to findings and results as noted below are preliminary and based on a limited number of subjects. Therefore, there may be differences as more subjects are recruited and included. However, interesting findings that show statistical significance are noted.

OVERNIGHT PSG REPORT

Comparison of control versus fatigued group shows that on the basis overnight basic study report, that includes parameters of numbers of respiratory events (apneas and hypopneas), leg kicks, sleep efficiencies, total sleep time, sleep efficiency, REM latency, wake after sleep onset, and arousals most did not show a difference between active and control group. This is anticipated, as we did not expect to attribute the fatigue and other symptoms in GWI to just a primary sleep disorder such as sleep apnea or periodic limb movements of sleep. It also helps to know that the two groups do not have markedly different total sleep times, or time it takes to fall asleep, directing more toward other contributors of daytime fatigue and the many other symptoms one may have. The one difference that was noted thus far was in the number of EEG arousals during sleep. Interestingly, there were more EEG arousals in the control group than the active group (on index—events/hour, spontaneous arousals, and total arousal count), with an index of 17.9 arousals/hour in the control group compared to 6.6 arousals/hour in the active group ($p=0.03$). We are in the process of looking at how both of these arousal numbers compare to a typical population, and reports in literature and our lab show about 16.5 arousals per hour common at this age group of 41-50 year olds. Arousals are actually not uncommon and may be occurring to a lesser frequency in the veterans with GWI, maybe due to the level of fatigue, or potentially this lower arousal amount at night is a continuation of 24 hour day condition of lower arousal, and one of the reasons veterans with GWI endorse not feeling alert in the day. This may be a substantial finding, different than models such as insomnia contributing to poor sleep, where hyperarousal in sleep may contribute to increased numbers of arousals.

t-Test: Two-Sample Assuming Unequal Variances

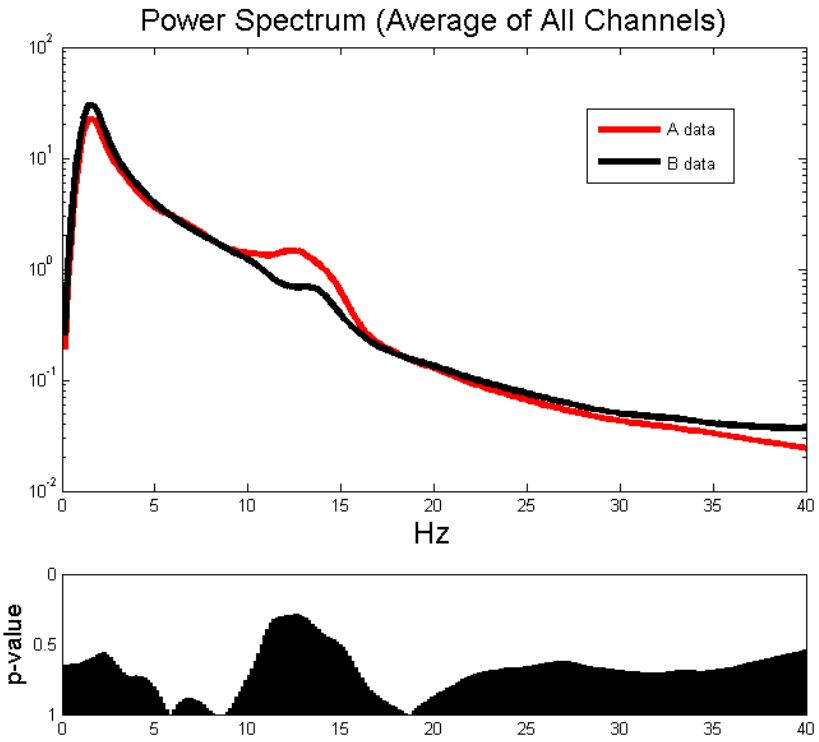
	Variable 1	*Variable 2*
Mean	17.8825	6.6
Variance	75.14723	17.81
Observations	4	9
Hypothesized Mean Difference	0	
df	4	
t Stat	2.475894	
P(T<=t) one-tail	0.034256	
t Critical one-tail	2.131847	
P(T<=t) two-tail	0.068512	
t Critical two-tail	2.776445	

Arousal Index (arousals per hour)

EEG ANALYSIS

The EEG data is in the processing/analysis stage. Detailed EEG analysis of our limited data includes overall topography data as well as power spectrum data averages. As we are still recruiting, data is preliminary and often not expected to reach statistical significance. We have processed all additional subject and not done further analysis at this point until we get a few more subjects.

The most recent source analysis shows that there is not a significant difference in the average of all channels for all frequency ranges. There was a slight difference in the slow wave spectrum (1-4 Hz), again across the whole night with all channels, which was not significant at this point. There were also some non significant differences in the 10-15 cycles per second range (seen in following figure), which is the range of sleep spindle activity, which are characteristic aspects that define clinical stage 2 sleep and are generated by thalamic and corticothalamic activity.



In looking at all NREM sleep through the night, while no channels are significantly different in absolute SWA, when overall SWA is taken into account comparing across all night, the fatigue group has relatively more slow wave activity in the right tempoparietal channels as noted in the following figure.

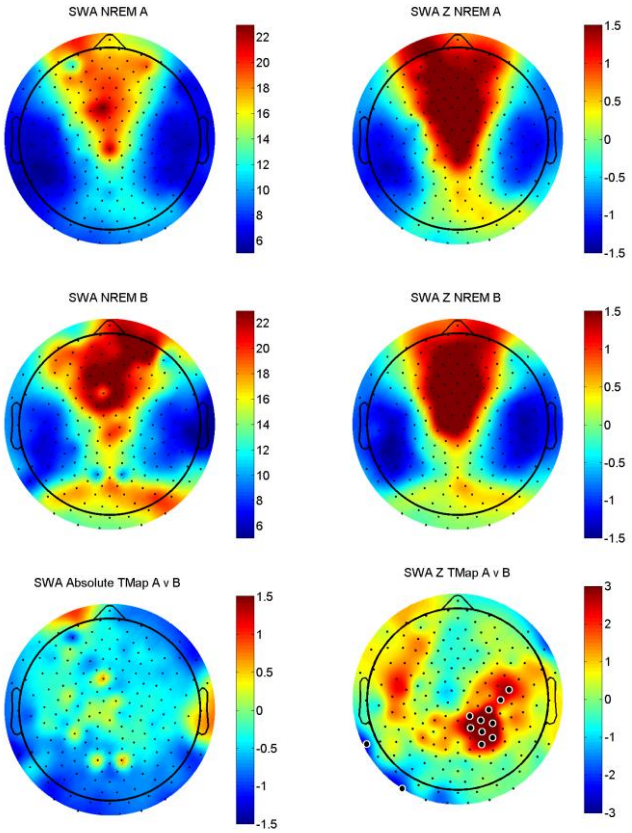


Figure : Absolute (left) SWA (1-4Hz) topography and spatially normalized (Z-score normalization, right) SWA topography for Group A (top row) and Group B (middle row). Uncorrected T-values (based on individual channel comparisons, bottom row) reveal that although there is no difference in absolute SWA, when overall SWA is taken in to account for each subject (normalized values, bottom right) Group A has relatively more SWA in a cluster of right temporoparietal channels. Significant channels ($p<.05$) are indicated as larger black circles outlined in white.

Additionally, the time course across cycles may be different. In literature, SWA has potential roles in recovery after a day of wake, and may impact fatigue as well as cognitive symptoms. This finding will be further assessed and pursued as additional data is collected.

Other data points assessed will now be reviewed.

RATING SCALES
On rating scales, most showed differences between control and active groups at this point.
On the MFSI-SF SF (Multidimensional Fatigue Symptom Inventory-Short Form), one-tail t test showed a mean in the active group of 95.3 versus 74.3 in the control group (P=0.0033).

t-Test: Two-Sample Assuming Unequal Variances (MFSI-SF Multidemensional Fatigue Symptom Inventory-Short Form)

	Variable 1	*Variable 2*
Mean	41.3	19.75
Variance	95.34444	74.25
Observations	10	4
Hypothesized Mean Difference	0	
Df	6	
t Stat	4.065535	
P(T<=t) one-tail	0.003305	
t Critical one-tail	1.94318	
P(T<=t) two-tail	0.006609	
t Critical two-tail	2.446912	

Depression scale scores on the Beck Depression Inventory and the Hamilton Depression rating scale both showed increased depressive symptoms in the active group compared to controls. Neither of these scores were particularly high as we excluded people who would have had clinical depression scores. They still separated from each other statistically on t test ($p<0.01$). Part of this may be related to the questions on scales that are directly related to energy and fatigue, which, as anticipated, would be endorsed in our active group more than our control group. Also, as a group, one with chronic multisymptom illness would be more likely to have some symptoms on the depression scales.

Similarly, scores on the Beck Anxiety Inventory were also statistically different with means of 9.2 and 1.75 ($p=0.001$).

The FOS-Q (Functional Outcomes of Sleep- Questionnaire) showed significant difference as well (P=0.008), a tool designed to assess the impact on multiple activities of everyday living, and thus a reflection of impact on a person's life.

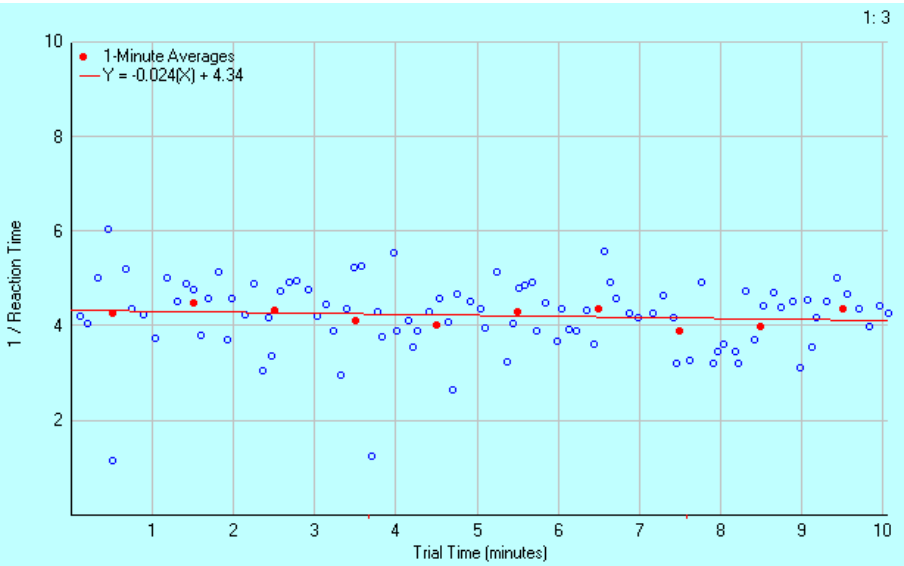
Epworth sleepiness scale did not show a difference. This is not suprising, as symptoms described by veterans with Gulf War Illness we interview typically are that of a feeling of fatigue and low energy and less likely literally falling asleep. The Epworth Sleepiness Scale measures sleepiness, not fatigue.

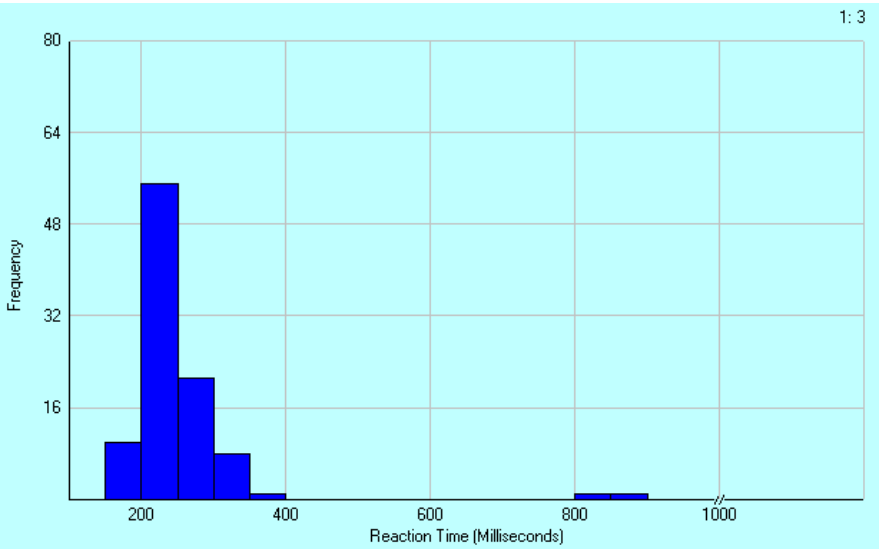
Brief pain inventory was near significance, with scores of 45 in the active group compared to 16 in the control group, p=0.058. Rates of some pain varied with some of the subjects in the control group, with some having pain but not fatigue or other multisymptom concerns.

Numerous other scales did show significant difference between the active and control group, and will be elaborated on as more subjects are added to the numbers.

PVT

PVT (psychomotor vigilance task) data is collected at multiple points in the study with subjective fatigue responses over a ten minute duration. We compared from various times, with levels of fatigue and between subjects when more data is available. The figure included below is for demonstration only of some of the responses on one PVT test on one subject.





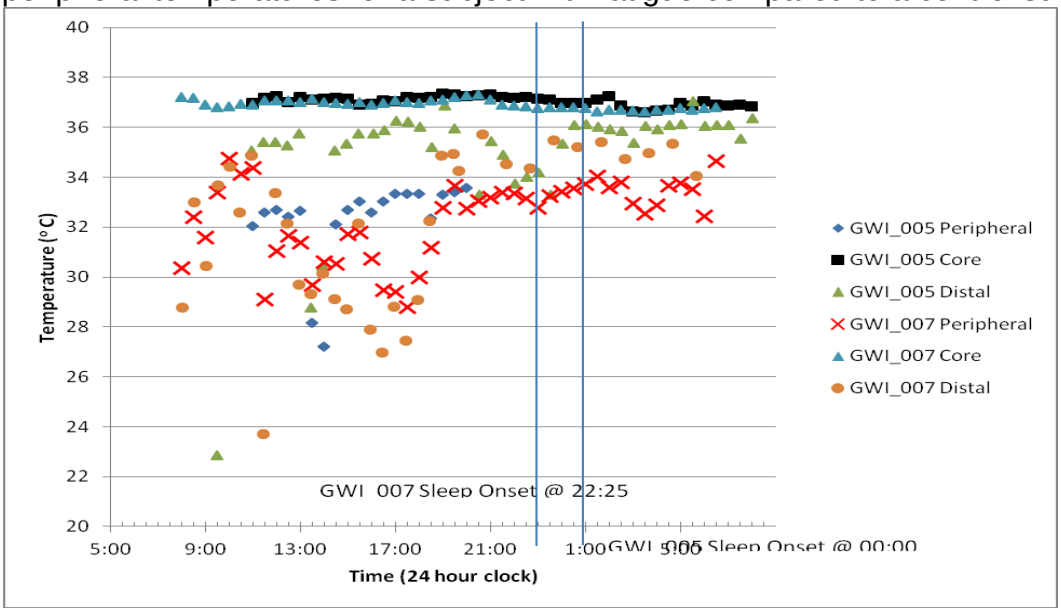
Psychomotor vigilance testing data, with comparisons of reaction time and numbers of lapses, there were not significant differences between the active and control group. This test does often show more robust differences in studies of sleep deprivation, where a person is sleepy and literally falling asleep related to such. In our study, we are not usually seeing people falling asleep more, rather finding that they have extreme fatigue and a low amount of energy to do things.

MELATONIN

We have samples of melatonin each hour for the approximate 6 hours prior to sleep. We are currently analyzing some of this data, and finding that there are clearly some subjects who do not have a typical pattern of low melatonin, then raised levels prior to sleep onset. Some have peaks much earlier, and some have less robust curves as far as amplitude is concerned. This interesting data as we collect more will help round out the picture noted about arousals and temperature.

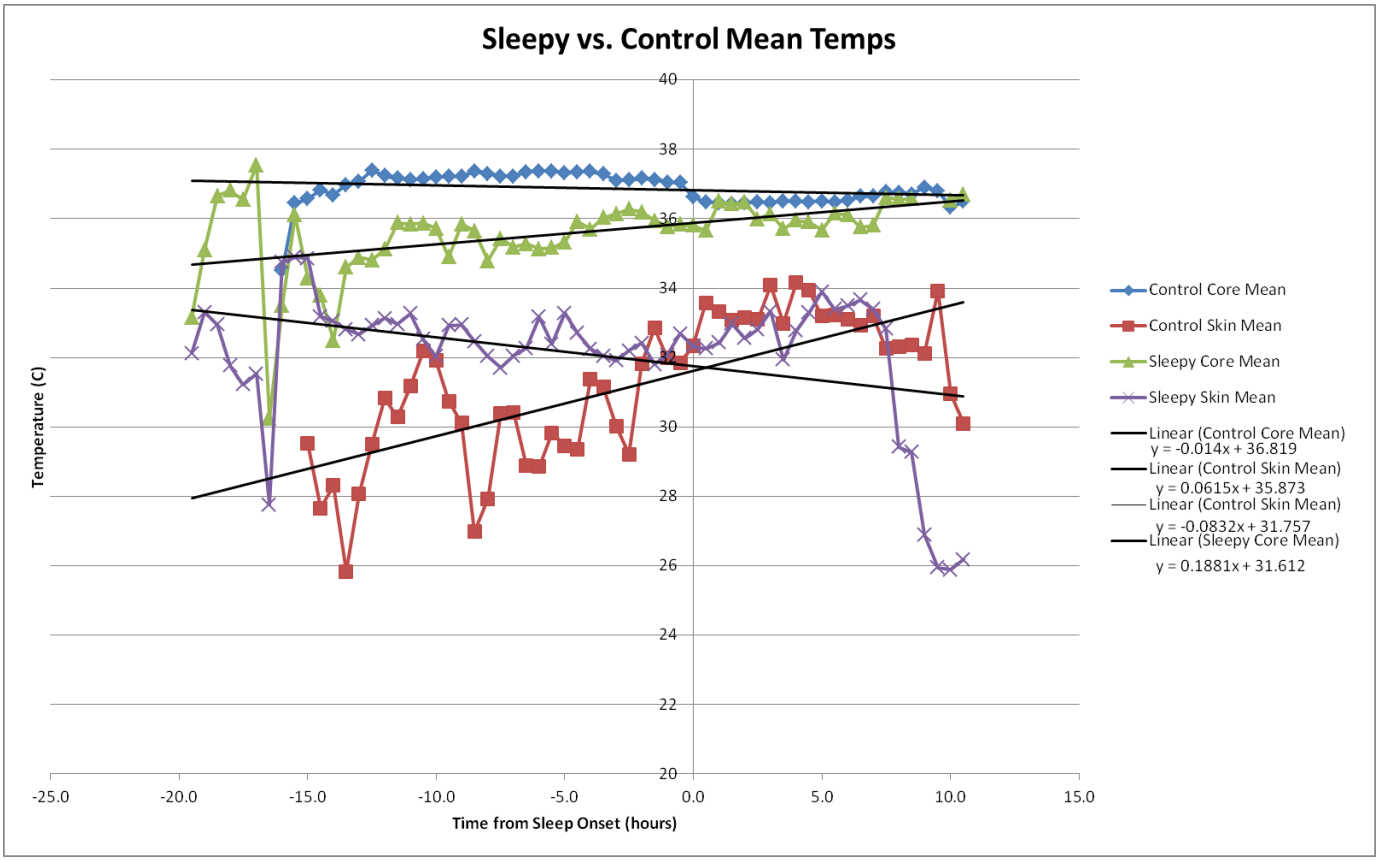
TEMPERATURE

Temperature findings are being processed. Below is a graph showing a curve for the core, distal and peripheral temperatures for a subject with fatigue compared to a control subject without fatigue.

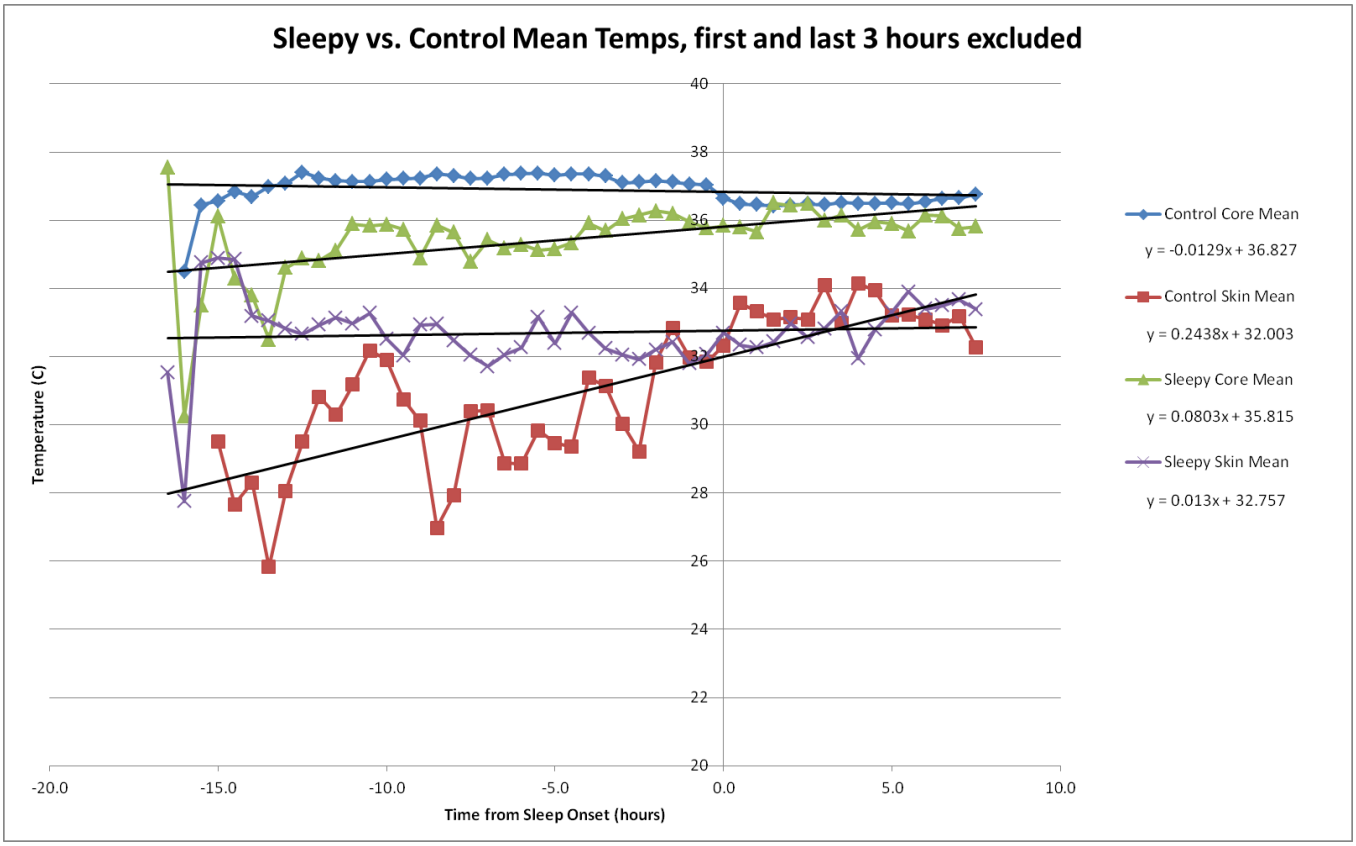


We have found differences in our control versus active groups in temperature measures thus far. A typical normal core temperature curve includes a peak several hours before bed and a nadir or low point shortly before waking. Our control subjects demonstrated this pattern. Our active group did not. Instead temperature change even had a slope in the other direction, when anchored to sleep onset time. Instead of being high prior to sleep onset, and low later in the night, they were lower to start with, with some increase in temperature over that time. Temperature and circadian rhythm are closely tied together. Alerting factors from the circadian rhythm may not be working properly for

subjects with this condition. The peripheral skin temperature is expected to move in the opposite direction to the core, as a way for the body to cool the core temperature by releasing that heat peripherally. We again saw the slope of that temperature change over time the opposite in veterans who endorsed fatigue compared to those who did not.



To try to account for potential noise in initial and final measurements, removing the first and last several hours of data showed similar results, though less robust.



CORTISOL

Cortisol samples have been collected and will soon be batch processed.

Key Research Accomplishments

Recruiting and data collection
Data processing
Some data analysis

Reportable Outcomes

Reportable outcomes have not yet occurred. We are currently in the data collection phase.

Conclusion

At this stage of data collection, substantial conclusions would be premature. However, we have shown that subjects who served in the first Gulf War who have extreme fatigue express that fatigue despite sufficient night sleep time, and time similar to those who do not have fatigue. We have demonstrated some differences on nighttime arousals during in a direction that may be counterintuitive when thinking of a subject with fatigue. However this may make sense and point in a direction different than an insomnia picture of less than optimal sleep. Further, temperature studies show differences, and can be a reflection of circadian rhythm abnormalities. Overall these 2 findings contribute to an overall picture of potentially lower arousal mechanisms day and night, with resultant feelings of fatigue. The topographic slow wave activity shows that while all NREM average amounts of absolute SWA are not different, there may be some topographic areas of differences. Also, the time course across the cycles with regards to SWA may be different. Further EEG analysis of other parameters in sleep is anticipated.

These finding offers some potential areas of future targeted treatments. Other potential contributors will continue to be assessed when they are analyzed (batched), such as cortisol and more melatonin.

References

Bonnett M, Arand D EEG Arousal Norms by Age. Journal of Clinical Sleep Medicine 2007 April 15;

3(3): 271-274.

Appendices

none